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Determination of the effect of the ultrasonic frequency on the cooling crystallization of paracetamol

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Abstract

This paper presents a study on the effect of ultrasonic frequency on both the nucleation and the degradation of paracetamol under sonication. The effect of ultrasonic irradiation was investigated for frequencies ranging from 41 to 1140 kHz. The results obtained in this paper show that the lower ultrasonic frequencies are preferable, both to enhance the nucleation rate and to limit degradation. A reduction of the metastable zone width was observed in all experiments when applying ultrasound. The highest reduction was achieved at a frequency of 41 kHz and a decrease of the reduction was observed with increasing ultrasonic frequencies. Degradation was limited at a frequency of 41 kHz, while significantly higher levels of degradation are observed at higher frequencies. Radical formation seems to be the main degradation mechanism for all frequencies.

Highlights

- Highest reduction in metastable zone width at the lowest frequency;
- Lowest degradation at the lowest frequency;
- Radical formation is the main degradation mechanism.

Keywords

sonocrystallization, process intensification, sonochemistry, sonochemical degradation, paracetamol

1. Introduction

Crystallization is a widely used technique for the production and separation of pharmaceuticals and fine chemicals [1-6]. The application of ultrasound in these crystallization processes has shown positive effects on the nucleation of both organic and inorganic components. Several papers report a reduction of the induction time at lower supersaturation levels, a reduction of the metastable zone width (MZW), the formation of smaller particles and an increase of the reproducibility of the particle size distribution after ultrasonic irradiation [3, 7-11]. Most of the sonocrystallization experiments reported in literature are performed in commercially available equipment with fixed ultrasonic frequencies ranging from 20 to 100 kHz [3, 12-15]. Because of this fixed parameter, the effect of it on the crystallization reaction is rarely investigated.

Only a few papers studied the impact of the ultrasonic frequency on the crystallization process. Li *et al.* tested the sonocrystallization of spectinomycin hydrochloride during ultrasonic irradiation at 15, 20, 25 and 30 kHz [14]. An ultrasonic horn with a titanium probe tip of 8 mm was used in a 15 mL solution. The power output was set at 400 W during all experiments. No significant differences in crystal size or shape were observed when varying these frequencies. Therefore it was concluded that all frequencies have the same influence on the nucleation and growth of the crystals. Somewhat higher frequencies were tested by Wohlgemuth *et al.* [16]. The impact of ultrasound at 204, 355.5 and 610 kHz on the MZW and crystal size distribution was investigated during the crystallization of adipic acid. A power of 200W was applied to an ultrasound transducer placed at the bottom of a 1.2 L reaction vessel. The transducer had a diameter of 100 mm. No dependence of the MZW on the frequency was observed, although smaller crystals are reported at lower frequencies. A bimodal distribution was visible in the graph of the particle size distribution. The second peak of the particle size distribution was shifted from 500 μm to 300 μm by varying the ultrasonic frequency from 610 to 355.5 kHz. This effect was explained by a reduction of agglomeration of the crystals at lower frequencies. It was assumed that the growth kinetics were changed by applying ultrasound, which resulted in changes in the crystal shape and consequently reduced agglomeration. It is, however, still unclear how ultrasound impacted the growth kinetics. Increased mass transfer due to enhanced micro-mixing under sonication is the most commonly used explanation in literature [17]. Kordylla *et al.* investigated the effect of the ultrasonic frequency and power on the cooling crystallization of dodecandioic acid [18]. Two different frequencies of 355.5 and 1046 kHz were tested in the same reactor setup as Wohlgemuth *et al.* The authors performed calorimetric measurements and it was observed that for the same power supplied to the transducers, the power inside the reaction medium was dependent on the applied ultrasonic frequency. The calorimetric power was therefore not constant between the different frequencies and no conclusions could be formulated about the effect of the frequency on the MZW. Furthermore, a decrease of the MZW was reported in the same paper with increasing power inside the reaction medium. The experiments were performed at output powers of 100 and 200 W for all frequencies. These observations, together with other papers about sonochemical reactions, show the importance of keeping the power inside the solution constant when comparing different frequencies [18-21].

Each of these three papers investigated the effect of the frequency on a rather limited frequency range. It could be expected that the effect on the type and size of cavitation bubbles is rather limited in this range [22]. Furthermore, it is difficult to mutually compare the results of these papers because of the different powers, products and reactor geometries. To make a general conclusion, the effect of the frequency should be tested with constant power in one reactor geometry on one product.

Besides an enhancement in crystallization, ultrasound is also capable of creating degradation. It is known that ultrasound can degrade organic compounds such as paracetamol [20, 23, 24]. Ultrasonic degradation can be caused by pyrolytic degradation of the investigated compound or via $\bullet\text{OH}$ radicals formed by implosion of the cavitation bubbles. The route of degradation is dependent on the physical and chemical properties of the organic compound. Volatile aromatic components undergo mainly pyrolytic degradation, while aromatics with hydrophilic characteristics are degraded predominantly via the radical chain mechanism. Isariebel *et al.* investigated the degradation of paracetamol by sonication in the frequency range of 574 to 1134 kHz and showed that degradation takes place by the reaction with radicals [20]. This reaction takes place at the interface of the cavitation bubble and consists of two steps. First $\bullet\text{OH}$, $\text{H}\bullet$ and $\text{HOO}\bullet$ radicals are formed within the cavitation bubble by the sonolysis of H_2O and O_2 . Secondly, these radicals move to the bubble interface to react with the organic compounds or they recombine to form H_2O or H_2O_2 . The degradation rate depends on the frequency as it impacts the amount of radicals formed inside the bubbles and released into the liquid. On the one hand, the cavitation effects are more violent at low frequencies, leading to a higher production of radicals. On the other hand, most radicals will recombine inside the cavitation bubbles at these low frequencies due to the long lifetime of collapse. At higher frequencies, the energy released upon collapse is reduced and consequently the yield for formation of radicals diminishes. However, the collapse occurs more rapidly and more radicals are able to escape from the bubble before they recombine. An optimum exists typically at a frequency between 200-600 kHz [24, 25]. During crystallization, this degradation is unwanted as the presence of impurities can create problems during the production of pharmaceutical components [5, 6, 26]. Significant inhibition or promotion of the crystal growth and the appearance of multiple nucleation bursts at the presence of even trace amounts of impurities are reported by Nagy *et al.* [5]. Consequently, these impurities can have a significant impact on the MZW and the size and shape distributions of the final products [4-6]. Therefore it is important to consider the influence of the ultrasonic frequency on the degradation of paracetamol during crystallization experiments.

The purpose of this paper is to gain more insight in the effect of the ultrasonic frequency on the nucleation of paracetamol. For the first time, the effect of ultrasound on the MZW was investigated within a broad frequency range of 41 to 1140 kHz in one single reactor geometry. In contrast to previously reported experiments, the power inside the reaction medium was kept constant for all frequencies. Furthermore, the sonochemical degradation of paracetamol was investigated under the same reaction conditions. Finally, the optimal ultrasonic frequency for enhancement of the nucleation was defined based on both results.

2. Materials and methods

2.1. Experimental setup

Figure 1 shows the setup which consists of a jacketed glass reactor without bottom plate, a top plate and ultrasound transducer. This transducer is placed at the bottom of the reactor and clamped to the top plate to allow proper sealing of the reactor. By clamping different transducers to the bottom, each operating at its resonance frequency, it is possible to use the same reactor over the complete frequency range.

Three different ultrasound transducers were used, one with resonance frequencies of 41 and 98 kHz (Ultrasonics World MPI-7850D-20_40_60H), another with a frequency of 165 kHz (Ultrasonics World MPI-4235D-235H) and a third with frequencies of 570, 850 and 1140 kHz (Meinhardt E/805/T/M). The first two transducers were glued to a glass plate to avoid corrosion and erosion of the transducer surface. The last one was a transducer with titanium diaphragm which could directly be used.

The ultrasonic frequency and power were controlled by a Picotest G5100A waveform generator which was connected to an E&I 1020L RF power amplifier which drives the ultrasound transducers.

The temperature was controlled by a Julabo FP45-ME thermostat bath and a Pt100 thermocouple. A Cole Parmer ultra compact mixer with axial blade impellor was used to stir the solution at 400 rpm.

2.2. Calorimetric measurements

First, the resonance frequencies of the transducers were defined by a Sine Phase impedance analyzer 16777K. During these measurements, the transducers were clamped to the reactor, 150 mL ultra pure water was brought into the vessel and the liquid was stirred at 400 rpm.

Second, the power dissipated to the liquid was calibrated for all transducers by calorimetry. The reactor was filled with 150 mL ultra pure water and insulated by fiberglass to avoid heat losses to the environment. Next, the temperature increase was recorded for 10 min at different input powers and the calorimetric power was calculated over these 10 min using Eq. 1.

$$\text{Eq. 1} \quad P_{cal} = \frac{dT}{dt} c_p m \quad [27]$$

with P_{cal} the calorimetric power (W), T the temperature (K), t the time (s), c_p the heat capacity of the solvent (J/(g K)) and m the mass of the solvent (g). The values of c_p and m were set at 4.186 J/(g K) and 150 g, respectively.

In all cases, a linear relationship between the power transferred to the transducer and the calorimetric power was observed with a linear correlation coefficient (r^2) of at least 0.989.

2.3. Measurement of metastable zone width

A 20 g/L paracetamol solution in water was created by dissolving 4g of 4-acetamidophenol (98% Acros Organics) in 200 mL ultra pure water. The solution was heated to maximum

80°C and stirred until all paracetamol was dissolved. Next, the solution was filtered over a 0.45 µm Millipore HAWP filter to remove solid impurities. Thereafter, 150 mL of the filtered solution was transferred into the reaction vessel. Care was taken to ensure that the temperature of this solution never decreases below 34.05°C, the saturation temperature of a 20 g/L paracetamol solution [28]. Samples were taken and analyzed on the HPLC to verify that the concentration was not changed during transfer. The temperature of the reactor was set at 40°C, 6°C above saturation temperature, and the stirring rate was kept constant at 400 rpm. At the start of the experiment, ultrasound was switched on and the solution was cooled at a fixed cooling rate of 0.7 °C/min. The voltage and power settings applied to the different transducers to obtain a constant calorimetric power of 8 W inside the reactor are listed in Table 1. From this table, one can see that for the same power inside the reactor, the electrical power sent to the transducers (P_f) should be different for the different frequencies. A similar observation was already made in literature by Kordylla *et al.* [18]. The power sent forward to the transducers (P_f) and the reflected power (P_r) are obtained from the amplifier. The calorimetric power was kept constant at 8 W to obtain an intensity of 53 W/L for all the different frequencies. The importance of these calorimetric measurements is already emphasized in literature [18, 20, 21]. It allows correlating the results solely to the frequency, and excluding the effect of difference in power input at each frequency. The point of nucleation was observed visually while the saturation temperature was taken from literature [28]. Fujiwara *et al.* [24] reported that visual detection of the nucleation temperature resulted in a maximum deviation of 0.41°C compared to other techniques such as focused beam reflectance measurement or ATR-FTIR, thus indicating sufficient accuracy for this study. Finally, the MZW was calculated as the difference between the nucleation temperature and the saturation temperature.

Differences in the surface roughness between the transducers are known to influence the MZW [26, 29]. Silent measurements, with the different ultrasound transducers at the bottom of the reactor in place, were therefore conducted prior to the sonicated experiments. These results were used as a reference to exclude the effect of the different bottom surfaces (glass or the stainless steel transducer) on the MZW. All sonicated and silent experiments were performed at least three times to ensure reproducible results.

2.4. Analysis of paracetamol degradation under sonication

Literature showed, that the degradation rate of paracetamol remains constant at concentration levels above 11 ppm [23]. At that level of paracetamol, all the hydroxyl radicals react exclusively with paracetamol. Therefore a concentration of 20 ppm was chosen to ensure that the maximum degradation rate was achieved and the detection of degradation products was still possible. First, a solution of 20 ppm paracetamol in ultra pure water was made. This solution was then transferred into the reaction vessel and heated to 40 °C. When starting the experiment, ultrasound was switched on and the solution was cooled at 0.7 °C/min to 20°C. In this way, the same cooling profile was achieved as during the tests of the MZW. 20°C was chosen as the end temperature because it was the average nucleation temperature observed during the measurements of the MZW. Next, the solution was kept constant at 20°C for 60 minutes, after which the experiment was stopped. Samples of 1.5 mL were taken every 10 min for HPLC analysis. An Eclipse XDB C18 - 4.6 x 150 mm, 5 µm column was used in an Agilent 1200 HPLC with a 90:10 aqueous solution of orthophosphoric acid (pH 2.2) : acetonitrile as the mobile phase at a flow rate of 0.250 mL/min. The injection volume was 10 µL and paracetamol was detected at a retention time of 10 min by the diode array detector

at 254 nm. Quantification was performed on the Agilent Chemstation software. The calibration curve for paracetamol showed a linear correlation ($r^2 = 0.999$) between the paracetamol concentration and the absorbance. The deviation between different injections was maximum 0.48%.

2.5. Analysis of degradation mechanism under sonication

Some additional tests were performed with 1-butanol to check the degradation mechanism of paracetamol. 1-butanol is known as a radical scavenger for the gaseous and interfacial region of the collapsing bubble [20]. A 22-fold molar concentration of 1-butanol (99.5 % Merck) was added to the solution of 20 ppm paracetamol in water. The same procedure as described in 2.4 was used during the rest of the experiment.

3. Results and discussion

3.1. Effect of the frequency on the metastable zone width

Figure 2 shows the average MZW and the standard deviation under silent conditions. Small differences are observed between the MZWs of the different transducers. Variations during nucleation or differences in the surface roughness between the transducers are known to influence the MZW [26, 29]. For each frequency, the results under silent conditions are used as reference values for further calculations to exclude these variations.

The reduction in MZW, calculated as the difference between the MZW under silent and sonicated conditions, is plotted in Figure 3. The results are obtained by keeping the power inside the reactor constant by means of calorimetry. Compared to the silent conditions, a reduction in MZW is observed for all ultrasonic frequencies. This reduction reaches a maximum of 17°C at a frequency of 41 kHz and diminishes with increasing frequencies. An almost linear trend between the reduction in MZW and the ultrasonic frequency is visible. These results deviate from previous papers which report no significant changes in MZW with varying frequencies [14, 16]. It is, however, likely that in these papers the power inside the reactor was not constant. Wohlgemuth *et al.* even mentioned a temperature rise, caused by applying ultrasound, between 0.5 K to 0.3 K when applying frequencies of resp. 204 and 610 kHz [16]. Besides the constant power used in Figure 3, the MZW is also measured over a much broader frequency range which allows clearer observations. The difference in MZW between the frequencies of 850 and 1140 kHz is still limited and the results show large variability at the higher frequencies. Comparing these results with the ones at 41 and 98 kHz shows, however, significantly higher reductions in MZW at the lower frequencies.

In figure 3, small standard deviations of 0.9 to 1.5 °C are visible at frequencies of 41 to 580 kHz. These values are considerably smaller than the 5.3°C and 3.9°C obtained at 850 kHz and 1140 kHz, respectively. It is hypothesized that low ultrasonic frequencies enhance the reproducibility of the MZW while higher frequencies yield values similar as under silent conditions. In literature, it is already reported, although without further explanation, that ultrasonic irradiation, mostly performed at 20 till 40 kHz, increases the reproducibility of the nucleation [3, 30]. As figure 3 shows that the effect of ultrasound on the MZW is less pronounced at higher frequencies; one could expect that the effect on the reproducibility also diminishes at these frequencies. Furthermore, it was observed that the standard deviations obtained at 850 and 1140 kHz approach the 4.0°C obtained under silent conditions.

Although the exact mechanism behind ultrasound nucleation is still unclear, there are some hypotheses reported in literature. The results obtained in Figure 3 are in agreement with two of these theories, but do not allow discriminating between them. Louisnard *et al.* proposed the hypothesis of segregation [31, 32]. This states that the solute and the crystal precursors are segregated, during a very short time, by the large acceleration of the cavitation bubble at the end of the collapse. Therefore, very high levels of supersaturation are created momentarily which enhances nucleation. The effect of the frequency on the segregation effect was simulated, and a reduction of this effect was observed at higher frequencies. This would mean that the effect of ultrasound on the nucleation is reduced at higher frequencies. The reduction of the segregation effect was explained by the decrease in the maximum bubble radius at higher frequencies, which in turn results in less violent bubble collapses [31]. The type of

cavitation bubbles is also dependent on the applied frequency. Transient cavitation events, where the bubble radius expands two to three times before implosion, are typically dominant at low frequencies. At high frequencies, stable cavitation bubbles are mostly present, leading to smaller oscillations of the bubbles around their equilibrium radius [33-35]. The simulations of this behavior are in agreement with the experimental observations obtained in Figure 3, as a decreased effect of ultrasound on the MZW was observed at higher frequencies.

The cavitation bubble as a nucleation center is another possible theory for ultrasound nucleation [36]. Foreign particles in a supersaturated solution are known to reduce the energy needed to cross the critical nuclei radius and hence creating heterogeneous nucleation [26]. This technique is often used in industry by introduction of seed crystals in a solution. Besides solid seeds, also gas bubbles can be used as foreign particles. Wohlgemuth *et al.* showed that the nucleation rate increases by introducing synthetic air bubbles in a solution of dodecanedioic acid and different solvents [36]. In this hypothesis of the cavitation bubble as a nucleation center, it is believed that cavitation bubbles act similarly as these seed crystals or gas bubbles [16, 36]. Furthermore, it was reported that the nucleation rate seems to depend on the size of the foreign particles. Cacciuto *et al.* simulated the effect of the radius of seed crystals on the nucleation [37]. Faster nucleation was observed when seed crystals with larger radii were added. This effect can be contributed to the contact angle between the molecule clusters and the foreign surface. Kordylla *et al.* showed that faster nucleation can be achieved when the contact angle is reduced [38]. Hence, it can be expected that larger foreign particles decrease the contact angle between the foreign surface and the clusters and consequently reduce the amount of work needed for nucleation. Since the size of the formed cavitation bubbles is inversely proportional to the applied frequency, this would mean that lower frequencies result in larger bubbles and consequently smaller contact angles and faster nucleation [15, 39]. Again, this is in agreement with the results shown in Figure 3.

3.2. Effect of the frequency on the sonochemical degradation of paracetamol

Figure 4 shows the concentration of paracetamol in function of the reaction time. A decrease of the concentration can be noticed for all ultrasonic frequencies, indicating that degradation occurs always to a certain extent. Ultrasonic irradiation at a frequency of 41 kHz shows the smallest decrease in paracetamol concentration, while the concentration was reduced the most at 165 kHz. The degradation rates are between $1.3 \times 10^{-7} \text{ M min}^{-1}$ at 41 kHz and $1.6 \times 10^{-6} \text{ M min}^{-1}$ at 165 kHz. These values are in the same order of magnitude as the $8.5 \times 10^{-7} \text{ M min}^{-1}$ reported by Jagannathan *et al.* [23]. In this paper, the degradation of paracetamol was studied in a 250 mL reactor at a frequency of 213 kHz and similar intensity of 55 W/L. The consecutive points in Figure 4, also show reproducible results in time. All data points at 165 kHz show the lowest concentration of all frequencies after the same irradiation time. Besides the point at 10 min, the opposite effect was observed at 41 kHz: the highest concentrations are always observed at this frequency. The same trend is visible in Figure 5, showing the degradation of paracetamol after 60 minutes of ultrasonic irradiation as function of the different frequencies. A degradation of 6% was observed during sonication at the lowest frequency of 41 kHz. This degradation reached at least 35% when applying higher frequencies. The highest degradation rates of 65% and 52% are observed at 165 and 850 kHz, respectively. These results correlate with the ones reported in literature. The frequency which yields the maximum degradation usually lies between 200 and 600 kHz [24, 40]. Petrier and Casadonte, for example, investigated the sonochemical degradation of 4-chlorophenol at frequencies of 20, 200, 500 and 800 kHz [40]. The smallest degradation was observed at a

frequency of 20 kHz and the highest one at 200 kHz. More elevated frequencies reduce the degradation rate further. Therefore, one can conclude that there is a higher risk at more elevated frequencies to form degradation products which can disturb the nucleation process and adversely affect the purity of the crystals.

Different peaks are observed when comparing the HPLC chromatograms of all the experiments. As an example, the chromatograms after 60 min of irradiation at 165 and 570 kHz are shown in Figure 6. The peak with a retention time of 10 min is paracetamol and the small peaks around 6 min are created by 4-aminophenol. It has already been reported that this component can be formed by the thermal degradation of paracetamol [41]. In Figure 6, peaks with retention times of 8 and 14 min are visible for the experiments at 570 and 165 kHz, respectively. All the experiments performed at a frequency of 570, 850 and 1140 kHz show a peak with a retention time of 8 min. This peak becomes visible 30 min after the start of the experiment and increases when time elapses. The experiments performed at 98 and 165 kHz first show a peak with a retention time of 8 min. After a while, a second peak with a retention time of 14 min appears and the first peak diminishes until it is not visible anymore. The experiment performed at 41 kHz shows no additional peaks, indicating that the amount of degradation products formed is rather limited. The identity of these different peaks is unknown but it is hypothesized that radical chain reactions are taking place in both cases but that the formed degradation products are different. Some additional tests with 1-butanol were performed to check whether the production of $\bullet\text{OH}$ radicals at the bubble interface was indeed causing the degradation at both 165 and 570 kHz. In Figure 5, the sonochemical degradation in the presence of 1-butanol at 165 and 570 kHz is shown. In both cases, the degradation was reduced to an insignificant amount compared to the degradation without the radical scavenger. This indicates that the sonochemical degradation occurs, for both frequencies, via radical chain reactions inside the cavitation bubble or at the interface of the bubble.

It should be mentioned that the reaction conditions during these sonochemical degradation tests are not exactly the same as during the experiments of the MZW. The used concentrations are 1000 times smaller to allow detection of degradation products with HPLC. Because of these low concentrations, no crystals are formed. It is difficult to estimate how degradation would occur when crystals are present, but it can be expected that the degradation occurs easier for dissolved products. Therefore, it is likely that the degradation levels measured during these experiments are an overestimation of the real sonochemical degradation during crystallization. The results obtained in this section give, however, a good indication of the effect of the ultrasonic frequency on the sonochemical degradation. These results can be important when very pure products are needed like for example during the production of pharmaceutical products. To the best of our knowledge, no publications are available in literature that report the effect of sonochemical degradation on the stability or toxicity of drugs. Few articles were found which use sonochemical degradation reactions to remove paracetamol or other drugs from wastewater [20, 42, 43]. In these articles, frequencies of 200 to 600 kHz are used and at frequencies beyond this range, the sonochemical degradation is considerably smaller. The formed degradation products are, however, hardly investigated. It is known that a whole range of nitrogenous and non-nitrogenous degradation products of paracetamol with varying toxicity and stability can be formed during the advanced oxidation of paracetamol with UV and H_2O_2 [44]. It is, however, not clear which degradation products will be formed during sonochemical degradation and which will be present in the final crystal. In addition, it is possible that by sonochemical degradation a product with a different

solubility is formed which will influence the MZW. No articles were found which investigated this possible effect.

The results obtained in Figures 5 and 6 indicate that the sonochemical degradation of paracetamol is caused by radical chain formation but that different degradation products are formed at frequencies below 165 kHz and above 570 kHz. It is, however, clear that low frequencies are preferable when degradation of paracetamol is to be avoided.

4. Conclusion

The effect of the ultrasonic frequency on the MZW and degradation of paracetamol under sonication was studied over a wide frequency range for the first time. The experiments were performed in a single reactor setup, with exchangeable ultrasound transducers. Unlike previous studies, the power inside the reactor was kept constant at 8 W by calorimetric measurements. In all cases, a reduction of the MZW was observed when applying ultrasound. The maximum reduction of 17°C in MZW was achieved at a frequency of 41 kHz. The reduction in MZW decreases with an increase of the ultrasonic frequency.

The sonochemical degradation of paracetamol was investigated under the same reaction conditions as the experiments of the MZW. The lowest degradation of 6 % was observed at a frequency of 41 kHz. Significantly higher degradation percentages, up to 65 %, were observed at frequencies above 41 kHz. The sonochemical degradation mechanism was identified by addition of a radical scavenger, 1-butanol. This showed that radical reactions inside the cavitation bubble or at the gas-liquid interface were degrading the paracetamol. However, different degradation products were observed for reactions below 165 kHz and above 570 kHz.

From the results obtained in this paper, it can be concluded that low ultrasonic frequencies are preferred for enhancement of the MZW. These low frequencies allow faster nucleation and lower sonochemical degradation of the products compared to more elevated frequencies.

Table 1. Input settings with V_{app} the voltage applied to the amplifier, P_f the power sent forward to the transducers, P_r the reflected power and P_{in} the difference between the forward and reflected power.

Frequency	V_{app}	P_f	P_r	P_{in}
kHz	mVpp	W	W	W
41	800	109	84	25
98	400	44	24	20
165	410	46	21	25
570	180	20	2	19
850	225	24	3	21
1140	210	24	5	19

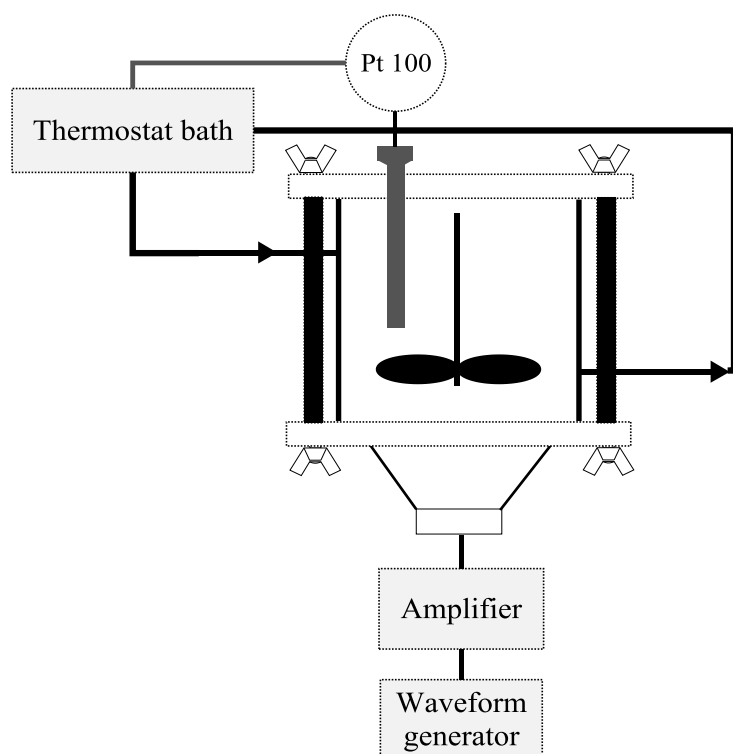


Figure 1. Reactor setup.

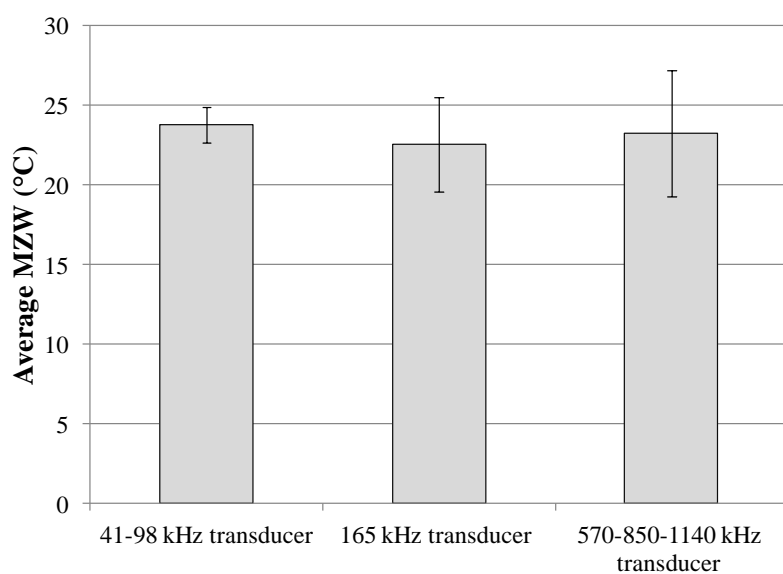


Figure 2. Reference MZW under silent conditions.

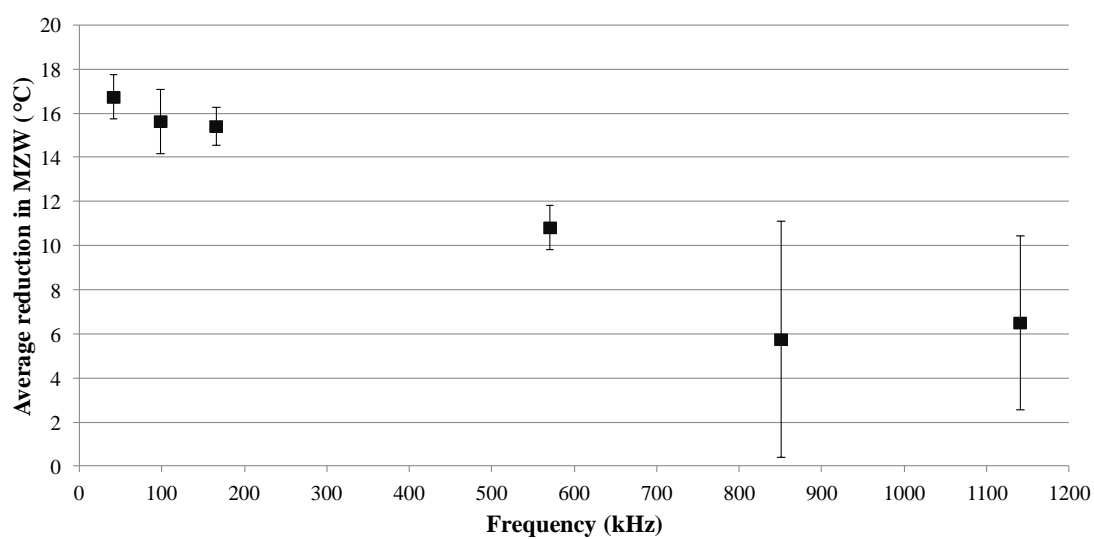


Figure 3. Reduction in MZW as function of the applied ultrasonic frequency. The dots represent the average reduction as function of the applied frequency and the error bars show the standard deviations.

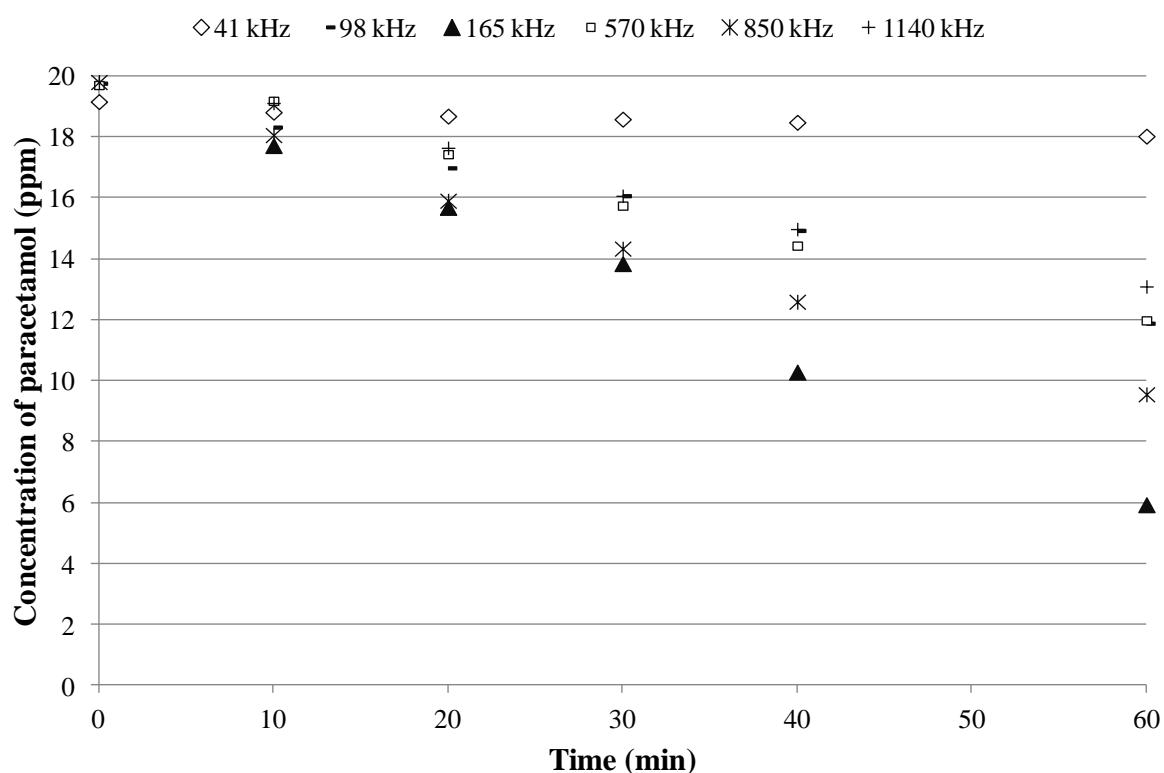


Figure 4. Concentration of paracetamol as function of time and frequency.

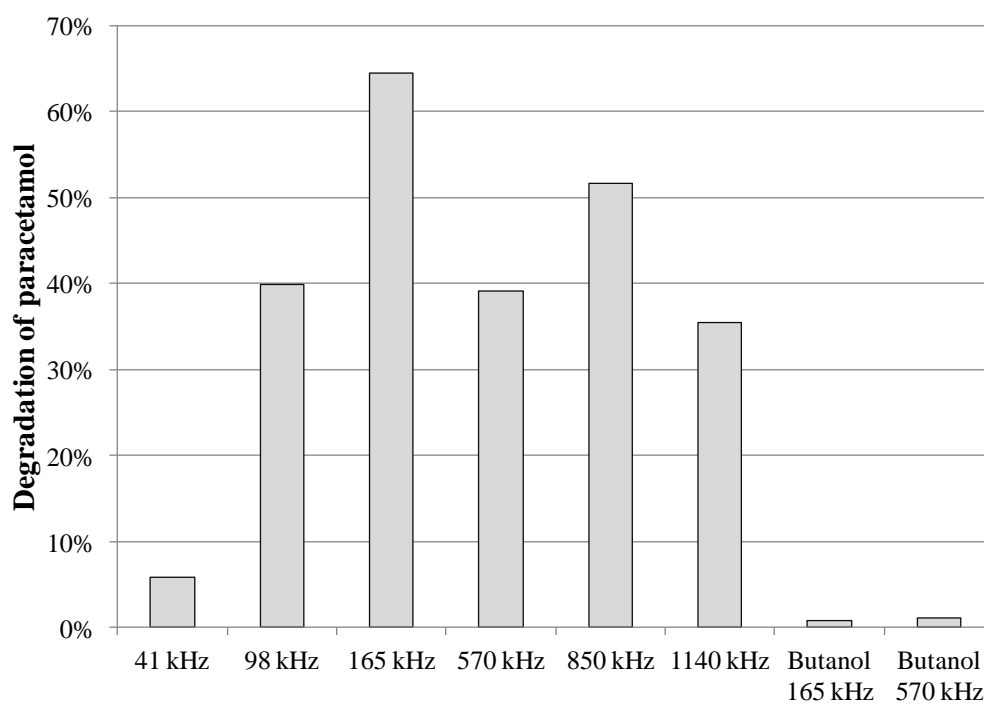


Figure 5. Degradation of paracetamol after 60 min ultrasonic irradiation at different ultrasonic frequencies, with and without scavenger.

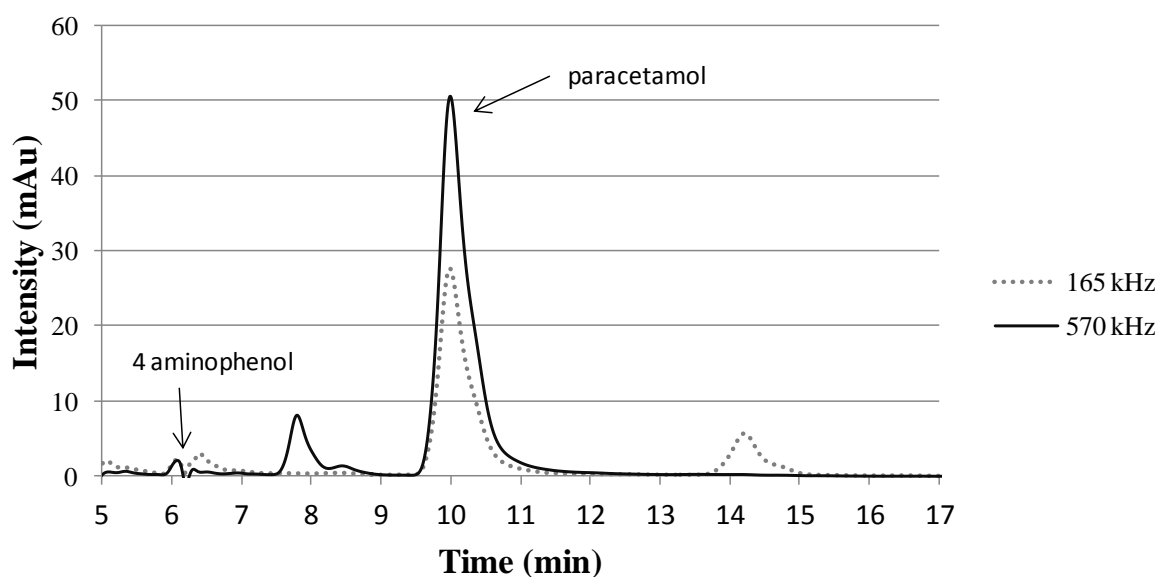


Figure 6. HPLC chromatogram after 60 min ultrasonic irradiation at 165 and 570 kHz.

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